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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/679,135	10/03/2003	David J. Pinsky	51917-CA-PCT-US/JPW/AJM/A	2202

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John P. White
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER	
PAK, JOHN D	
ART UNIT	PAPER NUMBER
1616	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/679,135	PINSKY ET AL.	
	Examiner	Art Unit	
	JOHN PAK	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46,49-62,65,89 and 90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46,49-62,65,89 and 90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/28/06, 8/14/06*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 46, 49-62, 65 and 89-90 are pending in this application. These claims will continue to be examined to the extent that they read on the elected subject matter of record. See the Office action of 6/26/2006, page 2, lines 2-6.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46, 49-62, 65, 89-90 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering carbon monoxide to an organ donor who is to be sacrificed after organ harvest, does not reasonably provide enablement for healthy donors who expect to live thereafter and organ recipients. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Instant claims encompass administering carbon monoxide (CO) to an organ donor who is not brain dead (e.g. healthy volunteer organ donor) and/or a recipient of organ transplant surgery. Even claims 89-90, which recite administering to a donor of the organ, do not exclude healthy organ donors or administering CO concurrently to the recipient of organ transplant surgery. This is the scope of the claims, which lack adequate enabling support.

The nature of the invention is directed to administering CO, a toxic gas, to vulnerable and compromised patients such as organ donors (not brain dead) or recipients of organ transplant surgery.

The state of the art regarding CO as a human therapeutic is still at a very early stage, even now, many years after applicant's effective filing date. "Despite the apparent success of CO therapy in animal models of lung injury, the utility of CO as therapy in humans remains elusive owing to difficulties in performing human experimentation." (**Ryter et al.**, 2006, page 260, right column; cited by applicant in the 8/14/2006 IDS). **Mayr et al**. disclose, "inhalation of 500 ppm CO for 1 hour did not significantly modulate systemic cytokine production as 250 ppm did in a murine LPS model. Hence, marked species differences must be considered when developing CO as a potential medicinal product." (2005, page 359, left column; cited by applicant in the 8/14/2006 IDS). **Dolinay et al**. disclose the following (2004, page 224, left column) (emphases added):

> Considerable obstacles remain before CO may reach clinical application, including political and regulatory approval, as well as social acceptance of a substance widely regarded as a poison. The duration and dose of exposure is still a subject of evaluation. It remains unclear how to define a safe dose of CO for human therapy. The toxicological consequences of low dose CO application remain incompletely understood. Alternative delivery approaches must also be considered, such as the injection of experimental CO releasing molecules.[147] Despite its reputation as a noxious gas, CO may be well on its way to providing a low cost and effective therapy for a number of disease conditions. Collectively, the body of research described herein heralds the future exploitation of CO in the clinic for the treatment of advanced-stage lung disease, and the improved success of organ transplantation.

Thom et al. disclose the uncertainty of those skilled in the art. Thom et al. state:

> Our main point is that there is a very real potential for unforeseen injury related to seemingly modest concentrations of CO. Additional information about CO pathphysiology is needed, **and it is premature to suggest clinical trials purposefully administering this agent to injured patients**.

(2005, page 1318, left column, last paragraph) (emphases added). Choi et al., in response to such comments by Thom et al., state (2005, page 1319, left column) (emphases added):

> We are aware of three ongoing human clinical trials for various pathophysiologic disease states where inhaled CO is administered at concentrations similar to those used by us (1). **Although it is unknown what results these studies will yield, we can continue to strive for additional and new knowledge to "tempt" us to speculate that some day inhaled CO could serve as a therapeutic modality in human diseases.**

The state of the art as discussed above shows a very high level of unpredictability. The amount of direction provided by the originally filed disclosure is in substantially similar language and scope as the instant claim language. Only animal (rats) test data is shown and there is no working example of human results. However, Mayr et al. and Ryter et al. are evidence that animal test data is not predictive of human therapy in this technology. Further, there is also no specific disclosure or working example of administering CO to a donor that is not to be sacrificed and there is no specific disclosure or working example of administering CO to a recipient of organ transplant surgery.

Therefore, one skilled in the art would be faced with undue experimentation to use the invention as claimed: various experimentation with humans and risking CO toxicity to vulnerable, injured patients and risking irreplaceable donor organs.

For these reasons, the claims are found to lack adequate enabling support.

Claims 46, 49-62, 65 and 89-90 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 46 was amended on 4/13/2006 as shown below:

46. (Currently Amended) A method for protectively treating a subject ~~at risk for~~ from an ischemic disorder as a result of organ transplantation which comprises administering to the subject via inhalation a gas comprising carbon monoxide in an amount and over a period of time sufficient to protectively treat the subject ~~for the ischemic disorder~~.

The Examiner's rejection of the claims is based on the following interpretation of the instant claims and originally filed disclosure:

Subject	Scope of instant claims	Originally filed Disclosure
Organ donor	Includes organ donor – see claim 90	Includes organ donor – see spec. p. 134
Organ recipient	Includes organ recipient because claim 90 shows that claim 46 encompasses more than just donor as the subject	Does not reasonably convey that the organ recipient is to be treated with CO also. See spec. p. 134, lines 4-34.

Applicant's invention with respect to organ transplantation is somewhat different in that a subject undergoing other types of surgeries is one and the same, whereas in organ transplantation surgeries, there are two subjects, the organ donor and organ recipient. In the originally filed disclosure, applicant does not explicitly disclose treating the organ recipient with CO in an amount and over a period of time sufficient to protectively treat the organ recipient. However, in the amended claims, applicant is now clearly claiming treating the organ donor as well as the organ recipient by virtue of distinguishing claim language – independent claim 46 reads on "a subject ... as a result of organ transplantation" and dependent claim 90 requires the subject to be the organ donor. Hence, claim 46 must necessarily encompass organ recipient because claim 90 is *further* defining the subject matter of claim 46. If only the organ donor were encompassed by claim 46, claim 90 would be superfluous.

It is the Examiner's position that the originally filed disclosure reasonably conveyed treating only the organ donor. The Examiner bases this determination from

applicant's failure to explicitly disclose treating the organ recipient with CO in an amount and over a period of time sufficient to protectively treat the organ recipient and applicant's exemplified characterization of ischemic disorders. On specification page 134, the following is disclosed about ischemic disorder and organ transplantation:

-134-

In the initial patent application, we revealed data indicating that endogenous production of carbon monoxide or administration of exogenous carbon monoxide is beneficial in protecting the brain against subsequent ischemic injury. As another example of the use of carbon monoxide in treating an ischemic disorder, we have administered carbon monoxide to rats to test its effects on improving lung preservation for transplantation (this is similar to an ischemic disorder, because the donor lungs are removed from a recipient; during the period in which the lungs are preserved and transferred from donor to recipient, there is an interruption in blood flow).

On specification page 135, the donor mammal is treated with CO:

Administration of Carbon Monoxide:
At the indicated time before surgery (4,8, or 12 hours), rats were placed in a bell jar, and carbon monoxide was administered at various concentrations (0.01%, 0.03%, or 0.1%), with the remainder of the gas mixture consisting of room air. (The gas was passed through a jar of water prior to administration, in order to humidify it for animal comfort). At the indicated times following initiation of exposure, rats were anesthetized and lungs harvested as described above. These donor lungs were used in subsequent lung transplant experiments.

Applicant thus conveyed in the specification that treating an ischemic disorder in organ transplantation surgery means improving organ preservation for transplantation. The protocol provided on specification page 135 adds to this understanding.

Therefore, the instant claims, which read on treating both the organ donor and the organ recipient, fails to find adequate descriptive support from the originally filed disclosure. The claims are thereby rejected.

Applicant's arguments and Dr. Kron's declaration of 12/28/2006 have been given due consideration but they were deemed unpersuasive. Applicant and Dr. Kron argue that explicit disclosure is not necessary for adequate descriptive support and the originally filed disclosure would have conveyed the subject matter of administering CO to an organ recipient undergoing organ transplant surgery. The Examiner cannot agree.

"Despite the apparent success of CO therapy in animal models of lung injury, the utility of CO as therapy in humans remains elusive owing to difficulties in performing human experimentation." (**Ryter et al.**, 2006). **Mayr et al**. disclose, "inhalation of 500 ppm CO for 1 hour did not significantly modulate systemic cytokine production as 250 ppm did in a murine LPS model. Hence, marked species differences must be considered when developing CO as a potential medicinal product." (2005). **Dolinay et al**. disclose the following (2004, page 224, left column) (emphases added):

> Considerable obstacles remain before CO may reach clinical application, including political and regulatory approval, as well as social acceptance of a substance widely regarded as a poison. The duration and dose of exposure is still a subject of evaluation. It remains unclear how to define a safe dose of CO for human therapy. The toxicological consequences of low dose CO application remain incompletely understood. Alternative delivery approaches must also be considered, such as the injection of experimental CO releasing molecules.[147] Despite its reputation as a noxious gas, CO may be well on its way to providing a low cost and effective therapy for a number of disease conditions. Collectively, the body of research described herein heralds the future exploitation of CO in the clinic for the treatment of advanced-stage lung disease, and the improved success of organ transplantation.

Thom et al. disclose the uncertainty of those skilled in the art. Thom et al. state:

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(2005, page 1318, left column, last paragraph) (emphases added). Choi et al., in response to such comments by Thom et al., state (2005, page 1319, left column) (emphases added):

> We are aware of three ongoing human clinical trials for various pathophysiologic disease states where inhaled CO is administered at concentrations similar to those used by us (1). **Although it is unknown what results these studies will yield, we can continue to strive for additional and new knowledge to "tempt" us to speculate that some day inhaled CO could serve as a therapeutic modality in human diseases.**

Thus, even many years after applicant's effective filing date, a person skilled in the art would not have recognized the subject matter of protectively treating an organ recipient subject undergoing organ transplant surgery by administering CO in the

absence of disclosure that specifically set forth such subject matter. The evidence set forth above sufficiently rebuts Dr. Korn's declaration.

For these reasons, this ground of rejection must be maintained.

After careful review of applicant's claim of benefit of earlier filed applications, the Examiner has not been able to verify the basis for granting benefit of the earlier filed applications PCT/US97/17229 and 08/721,447. This is critical because these are the only two applications that disclose CO for organ transplantation surgery. The Examiner's analysis is as follows.

35 USC 120 requires the application claiming benefit of earlier filing date in the United States to contain a specific reference to the earlier filed application. See also 37 CFR 1.78(a)(2)(i)-(ii). The reference must be submitted during the pendency of the later-filed application.

Since 08/721,447 was abandoned before the actual filing date of 09/671,100, the only way that applicant can obtain the benefit of its earlier filing date is if 09/671,100 contained a specific reference to an earlier filed application, which claimed the benefit of 08/721,447 and had copendency with 08/721,447.

Applicant asserts that this was accomplished by the first paragraph of the specification in 09/671,100. However, the first paragraph that applicant presents as

evidence was amended in 09/671,100 to read as shown below (amendment of 9/27/2000):

> On page 1, after the title and before line 5, please delete the paragraph and insert the following new sentence:
>
> --This application is a continuation of PCT International Application No. PCT/US99/07175, filed 1 April 1999, designating the United States of America, which is claiming the priority of U.S. Serial No. 09/053,871, filed April 1, 1998, the contents of which are hereby incorporated by reference into the present application.--

The prosecution history of 09/671,100 confirms that this is the correct continuation history and correct chain of claim of benefit, wherein the continuing data was corrected to read as shown ("Second Communication to Correct Error in Filing Receipts," page 2):

> --THIS APPLN IS A CON OF PCT/US99/07175 04/01/99 **WHICH CLAIMS PRIORITY OF U.S. SERIAL NO. 09/053,871 04/01/98**--
>
> Applicants contend that the correct continuing data may be found in the Declaration and Power of Attorney which was filed on December 6, 2000 in Response To October 6, 2000 Notice To File Missing Parts Of Application and in the Preliminary Amendment which was filed with the subject application on September 27, 2000. Copies of the Declaration and Power of Attorney and the Preliminary Amendment are attached hereto as **Exhibit A** and **Exhibit B** respectively. Accordingly, applicants request that a corrected Filing Receipt be issued.

Therefore, because 09/671,100 did not claim benefit of earlier filing date of 08/721,447 or PCT/US97/17229 and did not contain a reference to 08/721,447 or

PCT/US97/17229, the benefit of earlier filed to 08/721,447 or PCT/US97/17229 cannot be granted at this time.

Moreover, because none of applicant's other earlier filed applications for which benefit can be granted discloses administering CO to a subject undergoing organ transplantation, the earliest effective filing date that can be assigned to the instant claims is 10/3/2003, the actual filing date of this application. The consequence is that US 2003/0039638 is now available as prior art against the instant claims.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 46, 49-52, 54, 55, 61-62, 65, 89-90 are rejected under 35 U.S.C. 102(a) or (e) as being anticipated by Bach et al. (US 2003/0039638).

Bach et al. explicitly claim a method of transplanting an organ, the method comprising administering CO to an organ donor and transplanting the organ into a recipient, wherein the CO amount is sufficient to enhance survival or function of the

organ after transplantation (claims 1, 3-6, 14-24). The donor includes brain-dead donors (claim 3), and this ground of rejection is strictly limited to this scope so that this ground of rejection corresponds to the enablement rejection set forth above. Human donors are set forth (claims 23-24). CO is administered prior to and following brain death (claim 4), and CO can be administered to the donor before, during and/or after the step of transplanting the organ (page 1, paragraph 12). Delivery of CO in gas form is clearly disclosed (e.g. page 6, paragraph 93, lines 2-3; paragraph 105). Donor animal inhaling 1000 ppm CO gas is disclosed (page 28, paragraph 334-335). Transplanting the heart, pancreas, and liver are disclosed (claim 1).

Bach's disclosure meets applicant's claim language of "protectively treating a subject from an ischemic disorder as a result of organ transplantation" because removing an organ interrupts blood flow (see applicant's explanation of the same in the specification at page 134, lines 7-11).

Applicant's claim language of administering CO before and during the onset of the ischemic disorder is met by Bach's disclosure of administering CO before, during and/or after the step of transplanting the organ. The step of transplanting the organ is the ischemic disorder, according to applicant's specification.

All other features claimed by applicant are expressly taught, as discussed above. For these reasons, the claims are deemed anticipated.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 46, 49-62, 65 and 89-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bach et al. (US 2003/0039638).

Bach et al. explicitly claim a method of transplanting an organ, the method comprising administering CO to an organ donor and transplanting the organ into a recipient, wherein the CO amount is sufficient to enhance survival or function of the organ after transplantation (claims 1, 3-6, 14-24). Transplanting the heart, pancreas, and liver are disclosed (claim 1). The donor includes brain-dead donors (claim 3), and this ground of rejection is strictly limited to this scope so that this ground of rejection corresponds to the enablement rejection set forth above. Human donors are set forth (claims 23-24). CO is administered prior to and following brain death (claim 4), and CO can be administered to the donor before, during and/or after the step of transplanting the organ (page 1, paragraph 12). Delivery of CO in gas form is clearly disclosed (e.g. page 6, paragraph 93, lines 2-3; paragraph 105). 0.0000001 to 0.3% by weight of CO in a mixture with gaseous nitrogen and oxygen is disclosed (page 8, paragraph 105). Donor animal inhaling 1000 ppm CO gas is disclosed (page 28, paragraph 334-335).

Bach's disclosure meets applicant's claim language of "protectively treating a subject from an ischemic disorder as a result of organ transplantation" because removing an organ interrupts blood flow (see applicant's explanation of the same in the specification at page 134, lines 7-11).

Applicant's claim language of administering CO before and during the onset of the ischemic disorder is met by Bach's disclosure of administering CO before, during and/or after the step of transplanting the organ. The step of transplanting the organ is the ischemic disorder, according to applicant's specification.

Applicant's dependent claims 49-52 include CO at 0.1% in gas form. Bach et al. disclose 0.0000001 to 0.3% by weight of CO in a mixture with gaseous nitrogen and oxygen is disclosed (page 8, paragraph 105). Donor animal inhaling 1000 ppm CO gas is disclosed (page 28, paragraph 334-335). Applicant's concentration or sufficient amount feature is therefore fairly suggested.

Applicant's dependent claims 56-60 recite various period of time to administer CO, including up to about 1 hour to 1 day before surgery to up to about 1 hour to 1 day after surgery. Such period of time would have been suggested by Bach et al. because the administered CO is taught to enhance survival or function of the organ after transplantation. Prior to harvesting an organ, Bach et al. disclose treating with inhaled CO for 1 hour (paragraph 334). "Treatment should start as soon as possible following the declaration that brain death is present. In some applications, it may be desirable to

begin treatment before brain death." (paragraph 334). Therefore, the ordinary skilled artisan in this field would have been motivated to have the organ to be harvested treated with CO in situ in the donor at the claimed periods of time in order to obtain the effect of CO.

This is an alternative ground of rejection with respect to those claims that have been also rejected under an anticipation-based ground of rejection, supra. With abundance of caution, the Examiner has included said claims in this ground of rejection in the event that a position that Bach et al. do not provide a specific enough teaching to warrant anticipation were to prevail.

For these reasons, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention and the claimed invention as a whole have been fairly disclosed or suggested by the teachings of the cited reference.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to JOHN PAK whose telephone number is **(571)272-0620.** The Examiner can normally be reached on Monday to Friday from 8 AM to 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's SPE, Johann Richter, can be reached on **(571)272-0646**.

The fax phone number for the organization where this application or proceeding is assigned is **(571)273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

John Pak
Primary Examiner
Technology Center 1600